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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,075	07/13/2001	Avi Ashkenazi	10466/42	9210

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EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,075	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-46,49 and 52-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *44-46,49,57 and 58* is/are allowed.

6)☒ Claim(s) *52-56,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/18/4; 12/8/4*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on November 09, 2004 has been entered.

Response to Amendment

2. Claims 52-60 have been added as requested in the amendment filed on November 18, 2004. Claims 44-46, 49 and 52-60 are pending in the instant application.

Claims 44-46, 49 and 52-60 are under examination in the instant office action.

3. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed on November 18, 2004 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Information Disclosure Statement

6. The information disclosure statements filed on November 18, 2004 and December 08, 2004 fail to comply with 37 CFR 1.98(b)(5), which requires the following:

(5) Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication.

Applicant is advised that the information disclosure statement filed on November 18, 2004 has been considered in part. Specifically, the last reference ("NCBI, Nucleotide-nucleotide BLASTS") has not been considered. The information disclosure statement filed on December 08, 2004 has been placed in the application file, but the information referred to therein has not been considered (See MPEP 609, specifically III, C(1)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 52-56 and 59-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full length of the polypeptide of SEQ ID NO: 2, which inhibits VEGF stimulated proliferation of adrenal cortical capillary endothelial cells, does not reasonably provide enablement for any other molecular embodiment that lacks the amino acid sequence of SEQ ID NO: 2 and is associated with the formation or growth of lung or colon tumor. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 52-56 and 59-60 are directed to isolated polypeptides that are at least 80%, 95%, 99% identical to the polypeptide of SEQ ID NO: 2. The instant specification discloses that the instant polypeptide of SEQ ID NO: 2, PRO211, is capable of inhibition of VEGF stimulated proliferation of adrenal cortical capillary endothelial cells, which establishes the practical utility of the claimed protein of SEQ ID NO: 2. The instant specification further asserts that the instant PRO211 polypeptides are associated with the formation or growth of lung or colon tumors based on the data that DNA encoding PRO211 was amplified in samples of primary tumors and cell line models of lung and colon cancer (see Table 9, pages 229 and 231 of the instant specification and also page 7 of Applicant's Response of November 18, 2004). The Examiner maintains that the instant specification, as filed, fails to provide enough guidance for one skilled in the art on how to use the claimed polypeptides in the diagnosis or treatment of lung or colon cancer, thereby requiring undue experimentation to discover how to use Applicant's invention, as currently claimed (see also reasons of record in section 7 of Paper mailed on October 02, 2002 and in section 5 of Paper mailed September 03, 2003).

Applicant traverses the rejection by, first, referring to the analysis of the utility standards and quotation of appropriate case law and Examination Guidelines related to the issue of utility (pages 7-8 of the Response). Applicant's arguments appear to be misplaced because the instant claims were never rejected under 35 U.S.C. 101, lack of utility, and, therefore, the issue of practical utility of the claimed PRO211 polypeptides is not disputed.

Applicant further refers to three declarations filed in the instant application (pages 9-11 of the Response). Applicant submits that "[t]he Declaration by Audrey Goddard clearly establishes that the TaqMan™ realtime PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy and is in extensive use for the study of gene amplification" (middle at page 9 of the Response).

The Declaration of Goddard under 37 CFR 1.132 filed October 21, 2003 is insufficient to overcome the rejection of claims 52-56 and 59-60 because it establishes the validity of use of DNA as marker for cancer and the instant claims are directed to polypeptides. There is no information presented in the Declaration of Goddard that would state or suggest that if a gene encoding PRO211 polypeptide is found to be amplified in lung or colon cancer than the encoded polypeptide could be used as a marker for lung or colon cancer.

Applicant further refers to the Declaration of Avi Ashkenazi, which, according to Applicant "confirms that even in the absence of overespression of the gene product, amplification of cancer marker gene – as detected, for example by the reverse transcriptase TaqMan™ PCR or the fluorescent *in situ* hybridization (FISH) assays – is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer treatment" (bottom at page 9 of the Response).

The Declaration of Ashkenazi under 37 CFR 1.132 filed on October 21, 2003 is insufficient to overcome the rejection of claims 52-56 and 59-60 because: the main point that is presented in the Declaration of Ashkenazi appears to be that when a practitioner is treating a cancer patient, it is useful knowing that certain DNA of cancerous samples is amplified even if the level of expression of the encoded polypeptide is not changed, because the practitioner then

would adjust a treatment protocol by not treating the patient with agents that target that gene product. However, the Declaration presents only Dr. Ashkenazi's own reasoning and conclusions and fails to present any references to scientific publications or any evidentiary clinical support and, therefore, it's not persuasive (see *Meitzner v. Mindick,* 549 F.2d. 775, 782, 193 USPQ 17, 22 (CCPA 1977), "Argument of counsel cannot take the place of evidence lacking in the record").

At page 10, Applicant argues that "if a gene amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level" and refers to articles by Ornoft et al., Hayman et al. and Pollack et al. as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. This argument has been fully considered but is not considered to be persuasive for the following reasons.

Applicant characterizes Ornoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. However, Ornoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Ornoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region, which is highly amplified. Ornoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO211 in the instant specification. That is, it is not clear whether or not PRO211 is in a gene cluster in a

region of a chromosome that is highly amplified. Therefore, the relevance of Ornoft et al. is not clear.

Further, Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support enablement of use of the claimed polypeptides.

With respect to Pollack et al. publication, Applicant characterizes it as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the enablement of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, these publications do not appear to support the specification's assertions that the claimed PRO211 polypeptides can be used in the fields of cancer diagnostics and cancer therapeutics.

The Declaration of Polakis under 37 CFR 1.132 filed on November 16, 2004 is insufficient to overcome the rejection of claims 52-56 and 59-60 based upon 35 U.S.C. §112, first paragraph, for the following reasons.

The Declaration provides additional support to Applicant's statement that increase in the level of mRNA is predictive of corresponding levels of the encoded protein. However, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO211 in tumor samples as compared to normal samples. Only gene amplification data were presented. The Declaration of Polakis is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not to gene amplification levels and polypeptide levels. Furthermore, the instant specification, as filed, provides data showing a very small increase in DNA copy number. According to the information provided in Table 9, PRO211 DNA was found to be expressed at the level from 1.27 to 2.55 units in tumor primary samples and cell lines. There is no evidence regarding whether or not the PRO211 mRNA or polypeptide levels were also increased in these tumor samples.

Since the instant claims are directed to PRO211 polypeptide, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number approximately in half of the examined cases would be considered by the skilled artisan to be predictive of increased in mRNA and polypeptide levels. Article by Pennica et al. (PNAS, 1998, Vol. 95, pp.14717-22) shows a lack of correlation between gene (DNA) amplification and elevated mRNA levels (see page 14721, first column, for example). Also, Konopka et al. (PNAS, 1986, Vol. 83, pp. 4049-52) presents evidence showing lack of correlation between gene amplification and increased polypeptide levels (see abstract and the whole paper). Thus, providing how small was the increase of the PRO211 DNA copy number, and in view of the evidence provided by publications of Pennica et al. and Konopka et al., one skilled in the art would reasonably conclude that a small increase in gene copy number would not significantly

correlate with increase in polypeptide levels. One skilled in the art would have to resort to substantial amount of experimentation to determine whether or not the PRO211 polypeptide levels are increased significantly in the tumor samples and, further, if the levels of polypeptides with limited structural similarity to the polypeptide of SEQ ID NO: 2, also are increased. The instant specification, as originally filed, fails to provide any guidance or working examples on how to use the claimed polypeptides as markers for lung or colon cancer. Finally, it is noted that the Declaration of Polakis does not provide data such that the Examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide.

It is also noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research, 2, pp. 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one can not following the guidance presented therein and practice the claimed polypeptides without first making a substantial inventive contribution.

8. Claims 52-56 and 59-60 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Newly submitted claims 52-56 and 59-60 correspond to the previously examined and later cancelled claims 39-43 and 50-51 (see Applicant's statement at page 7, third paragraph of the Response). Therefore, the instant claims 52-56 and 59-60 are rejected under 35 U.S.C. 112, first paragraph for reasons of record as applied to claims 39-43 and 50-51 in section 8 of Paper mailed on October 02, 2002 and in section 6 of Paper mailed September 03, 2003.

Conclusion

9. Claims 44-46, 49 and 57-58 are allowed. Claims 52-56 and 59-60 are rejected.

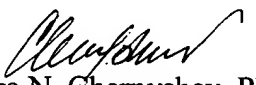
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (571) 273-0870. Official papers should NOT be faxed to (571) 273-0870.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1646

February 16, 2005